INFLAMMATION

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BY

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INFLAMMATION

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Dedicated to the
Members of the Wayne County Medical Association who gave service for their country in the World War.

JAMES A. MacMILLAN
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PREFACE

This monograph is the first of the Beaumont Foundation Lectures, given under the auspices of the Wayne County Medical Society on the thirtieth and thirty-first of January 1922, by William G. MacCallum, Professor of Pathology Johns Hopkins University.

This Foundation has been made possible by a fund set aside to the purpose of securing for the members of the Wayne County Medical Society annual lectures on some medical or scientific subject.

The plan is of noteworthy origin, for at the time of our entrance into the World War many of the society's members gave their services voluntarily to the cause. It became known that a number of these had family and other responsibilities requiring urgent financial assistance. To meet this need a patriotic fund was created by voluntary contributions from the members of the Society. This fund was purposeful in helping a number of physicians and their families through dark and trying situations. The total amount contributed grew far beyond the requirements and a very considerable surplus remained after all demands had been satisfied. This the contributors redonated to the progress of scientific medicine specifying the interest accumulation a reserve fund from which annual lectures should be secured. The Foundation was given the name of William Beaumont, in honor of a physician, now famous for pioneer research work begun at Mackinac, Michigan, in 1822, upon Alexis Saint

Martin. The clinical and laboratory researches accomplished were epoch making, giving to medicine new and valuable data upon gastric digestion forming the basis for all subsequent information upon the subject. The contribution was of signal importance, for it gave to medical science the biologic method of research which holds in relation to physiology a position analogous to that of dissecting to anatomy.

Medical history makes an enduring record not only of the great discoveries of Beaumont, but also of his wonderful devotion to a self-assigned task which he persistently followed under most discouraging conditions and great personal sacrifice.

The pursuit of truth and devotion to humanity are now as then at the basis of the art and science of medicine, and it is fitting that we commend the patriotism and generosity of the members of the Wayne County Medical Society whose contributions have provided in this permanent way a valuable asset to the medical work of Detroit.

It is the purpose of the Beaumont lectures to give instruction in the medical science and foster inspiration toward higher ideals. The lectures on Inflammation contain an orderly statement of the present day theories and demonstrated facts authoritatively stated and arranged in logical sequence and delivered in direct unambiguous phraseology.

J. A. M.
J. E. D.

INFLAMMATION

Introduction

Rather than attempt in the beginning any definition of inflammation it will be well to review our present knowledge of the subject and then in retrospect determine its outline. It may be said in advance that the conception of inflammation is an abstract one separating for consideration from all the endless series of inflammatory diseases that process which in principle and in the details of its character is common to all and in itself uniform in its broader lines. In whatever sort of injury, intoxication or infection it makes its appearance, we can recognise this process, which we name inflammation, as a reaction characteristic of the living body and little altered by the nature of the injury which causes the disease. It is one of many responses to injury at the disposal of the body, and useful in its defense. It becomes a part of our problem, therefore, to outline this particular reaction and in so doing to show its relation to the others. It is less a question of determining what features are essential to constitute inflammation (Aschoff) and more a question of deciding which of all the biological responses to injury ought to be grouped apart under this heading.

We think of inflammation then as a complex but orderly series of events forming a process well adapted to the defense of the body against the effects of an injury and evidently evolved and perfected in the

course of ages by selection and persistence of the most effective mechanisms which have arisen for the protection of the species. It is purposeful, not of course in the sense that the individual plans a reaction, but in the sense that through the wasteful phylogenetic method of the survival of those only that were best protected, the animal organism has acquired a well aimed machinery of defense.

From an historical point of view only two periods stand out very plainly after the age long recognition of the cardinal features of inflammation which were made precise by Celsus. Everyone knew in a general way the nature of inflammation and realised fairly clearly that it was associated with injuries of some sort. Everyone familiarly recognised the redness and swelling and heat of an inflamed member and felt the associated pain and disablement. John Hunter realised that while inflammation came with the most various injuries it often led to healing, but most persons even to this day, see little but evil in inflammation and strive toward its abatement.

Virchow's studies formed on the basis of the new cellular doctrine, were the starting point of accurate investigations, and Cohnheim's introduction of the experimental study of inflammation gave him practically all we now know of the process. Since then interest has waxed and waned with long intervals—curiously it comes in waves and all the old discussions are reopened. At present we are at the crest of a wave of such renewed interest and the literature—especially the German—is full of papers on the subject. It is true that many of these have a philosophical character and bring relatively few new facts to view, but some of them help to make clear our general conception.

Irritants and Injuries as the Cause of Inflammation

It has become clear from the study of innumerable instances of inflammation that there is always an underlying cause which is essentially an injury to the tissues about which the inflammation develops. We need not refer again to the beliefs of past eras when inflammation itself was regarded as a disease and indeed the most widespread disease in all the world, since we have learned that it is always possible to take a more comprehensive view of disease and analyse more clearly its origin, its progress and its termination. Nor need we dwell upon those curious statements as to the evocation of a true inflammatory reaction by hypnotic suggestion. In any case, if inflammation follows in a hypnotised person upon the application to the skin of a cold coin with the suggestion that it is red hot, it is the production of an injury which we are asked to believe—the inflammation might naturally follow.

Inflammation need not follow immediately upon the action of the injury—indeed, a certain time usually elapses before it develops fully and sometimes, as in X-ray burns, this delay may be rather long. But the delay is rarely such as to make it difficult to be sure that they are cause and effect. The variety of such injurious agencies is almost infinite. Among physical influences it is only necessary to mention the forms of mechanical violence which may compress, cut or bruise the tissues, extremes of heat or cold which can cause the death of cells or when less intense, their minor injury, the multifarious forms of light energy which injure and disturb cells in many ways and the types of radiant energy produced in the X-rays and radium which are no longer mere vibrations but

streams of particulate matter, and finally electricity which in various forms can injure and destroy tissue. Chemical agents of injury and destruction are even more varied and numerous and if we include among them the substances emitted by bacteria in the course of infections, their name is legion and their importance overwhelming.

But to all these injurious agents in their local action upon a tissue, the inflammatory reaction is scarcely specific. While there are some variations we are impressed by its uniformity under all conditions and we are impelled to ask whether after all it is primarily the injurious agent which causes the onset of inflammation, or the more invariable injured tissue itself. Nevertheless there are characteristic peculiarities in inflammations which are sometimes sufficient to suggest the character of the injurious agent and allow us to conclude with some certainty from the changes produced, that this or that form of irritant was at work. Still, this depends chiefly upon the character of the primary injury produced and very little upon changes in the inflammatory reaction and if we can distinguish a pneumonia caused by a virulent hæmolytic streptococcus from another caused by a pneumococcus, it is chiefly because of the extremely rapid destructive effect of the former organism, or if we can recognise the change in the mucosa of the stomach caused in one case by carbolic, in the other by sulphuric acid, it is less because of the character of the inflammatory reaction than because of the difference between the direct effects of these acids on the tissues.

The action of injurious agents in producing inflammation is a local action—and involves actual injury to the tissues. If a chemical substance such as hydrochloric acid be introduced in concentrated form into

the stomach, it injures the mucosa and excites inflammation but if it be so diluted as to resemble the gastric juice the whole quantity may doubtless be swallowed with perfect impunity. It is the local injury of the tissues which is essential to the explosion of the inflammatory reaction—and if through some other defensive reaction the injury is warded off—if the strong acid is washed or wiped away before the injury is effected—no inflammatory response follows.

It seems that the inflammatory reaction is not always commensurate with the injury and in this respect we meet with many difficulties which are not easy to explain away. A cinder in one's eye will stir up a more intense inflammation and more discomfort and pain than necessarily comes to one from the amputation of a leg by a competent surgeon. A blood vessel may be opened aseptically and half the blood drained away with little or no inflammatory protest to such an extreme injury although a few bacteria which reach the tiny wound may start a most violent reaction.

It seems that we have not yet adequately analysed the characters of these injuries which make for an inflammatory reaction. That they depend on the characters of the injurious agencies is obvious enough and the difficulty seems to lie to some extent in the separation of the local injury from the general one. But more especially it seems possible that there may be a distinction between injury and irritation. Usually both are present at once and one may mask the other. Thus a hot iron applied to the skin is intensely irritant and destructive at the same time. Mustard oil is somewhat destructive and very intensely irritating and its action on the skin is followed by an injury of moderate character and a very acute inflammation. Pure carbolic acid is also destructive, but while causing a deep

necrosis of the skin, anæsthetises it and is slowly followed by an inflammation which is less stormy than that produced by mustard oil.

Is it possible that the irritation which is felt by the nerves is capable of intensifying the inflammatory response, and is a painful injury more likely to be followed by inflammation than a painless one which destroys more tissue? The discussion of this question which cannot be very clearly answered, must be merged later with that of the part played by the nervous system in the reaction itself.

Direct Effects of Inflammatory Irritants upon Cells

It must be evident that in their action upon the tissues the injurious agencies which evoke inflammation must vary not only quantitatively but in the quality of their effects. Usually this effect radiates somewhat from the immediate point of impingement upon the tissue and becomes weaker and weaker as one passes out into the neighboring region. Every degree in intensity of the injury can be observed, therefore, in the margin of such an area and in many cases one can see the whole gamut of resulting alterations in the cells, from complete destruction in the centre to mild or fading disturbances of nutrition or function as the normal unaffected tissue is approached. Often the injury is so slight although followed by an intense inflammatory reaction, that it is difficult to see the direct effects in any cells. In many cases so few cells are actually killed that Neuman has suggested the term micronecrosis to express this condition. Even here, however, if the ultimate fate of these cells can be easily observed, their death becomes more obvious. A sunburned arm shows at first no clear proof that

cells have been killed but later when the surface skin peels off we know that those cells at least have been destroyed.

Interference with the life processes of cells may affect their function, their nutrition or their power of growth and division. Borst in his excellent paper, makes an effort to consider these separately and emphasises the importance of the integrity of the functional activity of the cell in the maintenance of the other activities. The most severe injury produces immediate death of the cell—anything short of this leaves the cell alive perhaps to die later or to live in a disabled state. Injuries of intensity sufficient to cause death of the cell may yet vary in quality so that while some, such as the application of a hot iron or pure carbolic acid coagulate the whole protoplasm at once, others may kill the cell without themselves producing coagulation. It is far more difficult to be sure that the life of a cell has ceased without coagulation. We cannot readily determine, for example, whether potassium cyanide in killing a cell has any coagulating effect because a cell, however killed, quickly becomes coagulated or causes the coagulation of the tissue fluids which permeate it by virtue of the ferments which it now liberates.

All functional and other cell activity stops with this fixation and the cell is as it were arrested as though suddenly petrified in what we have become accustomed to consider its normal state in our microscopical preparations of fixed tissues. In a man who had died promptly from the effects of swallowing a large amount of pure carbolic acid, the whole stomach was white and coagulated but in sections its mucosa presented the ideal picture of perfectly normal tissue.

When the coagulated cell remains surrounded by living tissue, however, protein-dissolving ferments

quickly change it so that the nucleus no longer takes the stain and the whole architecture of the cell is rapidly disintegrated. Dead cells thus soon melt into formless masses even when the injury itself does not mangle or deform them.

Less severe injury which does not interrupt the life of the cell also does not coagulate it but disturbs all its functions. Evidences of functional activity are not easy to observe unless we watch living cells. It is true that specific secretory granules should form an index of one sort of function but changes in them, as well as changes in the bulk of the cell, and the accumulation of other granules of questionable nature are hard to interpret.

Cloudy Swelling.—The whole question of cloudy swelling or parenchymatous degeneration comes to the fore at this point and must be discussed if only because of the part it has played in the history of inflammation. Virchow described it as an essential and prominent feature of inflammation. He saw in injured tissues when studied in the fresh condition, that the cells become greatly swollen and their special features such as the striated borders of the renal epithelium, obscured on account of the abundant accumulation of fine granules of protein substance in the cytoplasm. This he regarded as an accumulation of nutritive materials in the cell. For him inflammation was a disturbance of nutrition affecting especially the cells, which attracted nutritive substances to themselves. A fluid protein containing exudate accumulated between and in the cells, producing in both places the swelling which in an inflamed area becomes evident to the eye. In this exudate and between the cells new cells formed which were leucocytes. This theory has been abandoned but its main idea, that upon injury, the cells of the tissue actively respond and defend themselves,

swelling up and accumulating protein granules and fluid, has continued to interest some investigators who even now attempt to resuscitate the idea of a parenchymatous inflammation, in which the changes in the fixed cells are to be interpreted as the expression of their energetic attempt to defend themselves and the other cells against the damage.

But nearly all pathologists look upon these changes as retrogressive in character—the effects of the injury sometimes ending in disintegration of the cell but often less severe and fading away with the recovery of its full function. v. Hansemann dwells particularly upon the importance of a proper understanding of cloudy swelling which he thinks has been greatly neglected but he does not revert to the theory of its paramount interest as an active process. He explains that the "*tröpfige entmischung*" of Albrecht is something quite different and that one can observe the true cloudy swelling only in teased preparations or frozen sections of fresh unfixed tissue. Fixed tissue is confusing, for even formalin contains enough acid to dissolve these granules promptly and to produce by coagulation other granules which may be mistaken for them. Marchand, on the other hand, would abandon the term cloudy swelling as having no precise meaning since much of the granular material found in cells is due to post-mortem changes, other granules are really minute fat droplets, while the condition in one organ may represent something quite different from what in another organ produces the same appearance.

Most interesting in this regard because based on a really trust-worthy method of study, are W. H. Lewis' observations upon the granules which appear in dying cells in tissue cultures. These are minute or larger granules arranged chiefly about the centriole often in vacuoles and staining red with neutral red, while the

mitochondria take none of this stain but are colored by Janus black. He regards them as waste products of the cell and not as enclosed food particles. R. Prigosen, working under Lewis, makes similar observations for other cells under abnormal conditions which lead to their degeneration.

It is scarcely possible to be quite sure that these granules correspond exactly with those seen in cloudy swelling but the thought suggests itself and if one transfers their conclusions to this condition it would seem that in cloudy swelling one might regard the granules as waste products not especially indicating a disturbance of the function of nutrition to which some authors have ascribed an accumulation of unused foodstuffs within the cell.

Fatty Degeneration.—It is not any more simple to decide as to the relation to the functional capacity of the cell of the excessive amounts of visible fat in the form of globules which are so often found in injured cells. The divergent opinions about this are well known and it has always seemed more rational to suppose that in an injured cell the ability to digest and utilize fat naturally brought to it is impaired and that therefore the fat is formed at the expense of the cytoplasm. There is, of course, the view that since it is well known that the tissues contain much fat in invisible form, its occurrence in globules is merely a collection and rendering visible of fat already present (fat phanerosis). At any rate, there is practically no doubt that in injured cells the fat becomes conspicuous as an evidence of injury and persists even if the injury progresses to the death of the cell. But that such cells need not die is evident from observed recoveries and from the fact that in a liver in which a zone of each lobule is rendered necrotic by some poison, the cells of adjacent zones become loaded with

fat, and it is precisely in those less injured fat holding cells that regenerative mitoses are seen.

Other paraplasmic substances such as globules of hyaline or fibrinoid material may accumulate in large swollen and injured cells. Vacuoles without any content other than fluid may also appear. Glycogen in increased quantities in the less deeply injured cells is an accompaniment of the inflammatory reaction (Best).

Interpretation of Effects of Injuries.—The significance of all these accumulated materials is in each instance difficult to decide. We know that they accompany injury but it is not perfectly clear whether they are passively collected as the result of a degradation in the functional capacities of the cell or possibly evidence of an attempted active response on the part of these cells—a defensive response against the injury.

To me it appears that the evidence is overwhelmingly in favor of the view that they are merely signs or indications of injury associated with other and more unmistakable evidences of injury as time passes and the cell proceeds to disintegrate. Evidences of active response exist, it is true, in the rapid growth and reproduction of the leucocytes and possibly there may be a new formation of other more locally formed cells with a defensive significance. This, however, is the most bitterly debated question in the whole story of inflammation and must be deferred to a later point. Epithelium, muscle, nerve cells, etc., seem little if at all specialised toward defensive activities and although they show signs of regeneration after injury they proceed timidly and only after the way has been cleared of danger.

Retrogressive changes are produced, also, in the more hardy elements upon which these cells rely for their defense—in the blood-vessels, the connective

tissue and in the leucocytes, and like the others, they die or degenerate and the capillaries are obliterated, but the next ranks are still alive and active in spite of slighter injuries.

Direct effects of injuries thus vary in intensity and extent with the nature of the injurious agent and with the degree to which it is allowed to act. In the case of bacterial infections the injury may grow in proportion with the failure of defense so that the invasion of bacteria promptly halted by the tissues of a normal person before the bacteria have an opportunity to multiply, becomes in a weak old man an overwhelming spread of bacteria throughout the body, and a hopeless rout for the defense.

General illness following an injury must be regarded as the direct effect of the injury and cannot be ascribed to the defensive reactions, inflammation, fever, etc.. This will become clearer as these reactions are described.

The Inflammatory Process

In a general way everyone is familiar with the appearances of inflammation, with the redness and irritation and tenderness or actual pain in the hot swollen place, and everyone looks for a cause of one sort or another. But to search beneath the surface and to analyse into its elements this peculiar and complex change has required the concentrated study of many years with many problems still left unanswered. Virchow attempted it as related above, with the result that he found the fluid exudate among the cells with many leucocytes and a swelling of the cells with abundant granules in their cytoplasm. He recognized the hyperæmia but thought the leucocytes were formed by multiplication between the fibres of the tissue and that the swollen cells were of all things most active in this process.

The Vascular Reaction.—It was then that Cohnheim conceived the idea of exposing transparent vascular tissues such as the mesentery of the frog, or its tongue, from which the epithelium had been stripped off, to continuous observation under the microscope and quickly discovered the marvellous happenings which have ever since been so familiar to all who study inflammation. It may be wearisome to have all this rehearsed but without it we can scarcely proceed to any of the details which have since been added.

The mere exposure to air is sufficient to irritate and injure the mesentery of the frog so that inflammation begins very soon but with such a tissue as the web of the frog's foot or the wing of a bat it is necessary to apply an irritant to attain the same result. Too severe an injury will cloud the view because it may produce too profound changes in the tissues and blood vessels, so that the circulation is stopped in the field of observation and the tissue dies—it is then only in the surrounding areas, sometimes quite far away, that the process of inflammation is clearly to be studied, and with the mesentery of the frog, and far more with the mesentery or omentum of a warm-blooded animal, great care must be used to protect the tissue against drying and against extremes of temperature lest the injury be too complete.

The circulation in arteries, capillaries and veins can be seen with great clearness and its rate and volume easily observed. The arterial blood goes rapidly in pulsations but through the capillaries and on into the veins it is slowed into a steady stream in which one may see that the flowing cells maintain a central or axial position everywhere separated from the wall by a zone or layer of clear plasma. The surrounding connective tissue cells and fibres are in their normal relations. Very soon it is realised that the stream is hurry-

ing at a more rapid rate and that the arterioles and venules have widened noticeably. The blood rushes through the dilated capillaries and into the venules so fast that there is no possibility of recognising in the yellow stream any separate cells. But then, with a further widening of these vessels and the appearance of new wide capillaries which were invisible before, the voluminous stream begins to go more slowly and still more slowly until one may actually see the red corpuscles as they pass. In some channels it may even stop for a time only to move on again or finally to come to rest. But in general, apart from such minute stases, the stream goes on slowly and one can see that in the plasma zone against the vessel wall there collect leucocytes which roll along, sometimes sticking to the endothelium and being dislodged. A glance at the connective tissue outside the vessel shows that a change has taken place there, for now the cells and fibres are spread apart by fluid which has collected between them having filtered out through the walls of the capillaries.

Emigration of Leucocytes.—Continued watching shows, as Cohnheim described it, somewhere along the wall of a minute venule a tiny projecting point of clear protoplasm which grows until finally it pulls itself away from the wall and drops apart as a rounded, glistening cell—nothing other than a leucocyte. It moves away a little and many others worm their way out through the wall in the same way and accumulate about the vessel or near it. This, the emigration of the actively motile leucocytes, is the crux of the whole beautiful observation but from the way he describes the effect of stopping the flow of blood in checking the emigration, it seems that Cohnheim did not clearly recognise the independent activity of these cells but thought they were forced out by the pressure of the

moving stream. This explanation he applied to the red corpuscles too which may follow out in small numbers in the wake of the leucocytes. When the injury is very severe and the stream tends to stop, there is no chance for the selection from the blood of the relatively less numerous leucocytes and a great excess of red corpuscles is extravasated—this is the hæmorrhagic inflammation that comes with some very intense bacterial infections.

The Exudate.—Thus, there are now among the cells and fibres of the tissue many leucocytes and perhaps a few red corpuscles which are left quite near the vessels while the leucocytes wander farther afield. Being injured, the cells furnish a ferment to the coagulable fluid and a delicate meshwork of fibrin appears among the separated fibres of the connective tissue. With the aid of staining methods or even in the living tissue, one can see a few other cells loosely scattered in this oedematous tissue which vary in size but differ from the leucocytes in having a single rounded nucleus and few cytoplasmic granules. These monunuclear cells which seem to wander in from the neighboring tissue are few at first but in protracted inflammations become very numerous.

Thus we have a new condition in which the whole vascular bed is widened, blood is brought in increased quantities to the part and much of the contents of the vessels is poured out to bathe the injured tissues. These changes quite readily explain the cardinal symptoms of inflammation—the redness, the swelling and the heat of the inflamed place which, from being so flooded with blood, assumes the temperature of the interior of the body.

Discussion of the Factors in the Inflammatory Process

The Hyperæmia.—The first phenomenon which re-

quires explanation is the active hyperæmia which can perhaps be separated although by no very sharp line, from the later hyperæmia in which the vessels seem paralysed. It is marked by a rapid stream through somewhat widened channels and one might think of it naturally as a vasomotor phenomenon through irritation of the nerves. Much interest has been centred in the relation of the vascular changes in inflammation to the nervous system in recent years but even yet this relation is not perfectly clear. I myself found that if the leg of an animal were completely amputated and then replaced by anastomosis of the large vessels and suture of the other tissues so that one might be certain that all nerves of whatever character were cut, the application of mustard oil produced inflammation of quite as pronounced character in the amputated leg as in the normal one. It appeared at the same time and was if anything slightly more intense. A. Ninian Bruce confirmed this and ascribed the vascular widening still to a vasomotor effect produced as an axone reflex by which he meant that sensory stimuli were transferred to efferent vasomotor fibres at some point along the sensory nerve axone without recourse to the brain or cord. He found, however, that if the nerves be allowed to degenerate after section, no such arterial hyperæmia occurred. So, too, Breslauer found that the initial active hyperæmia followed for a time after the nerves were cut but later, after the nerves were degenerated, failed to appear upon the application of the irritant. General anæsthesia had no effect upon the appearance of this hyperæmia but local anæsthesia abolished it. In contradiction of Spiess' results he found that the central appreciation of pain from peripheral stimuli had nothing to do with inflammation. On the other hand, Groll finds that the reflex production of hyperæmia plays no part—the appearance

of an irritative arterial hyperæmia is not interfered with by nerve section even with degeneration. The nervous system affects the inflammation only indirectly by affecting the circulation, and the changes in the inflamed area are due to direct action of the irritant.

Thus, it seems that the ideas about the relation of the nervous system to the dilatation of the arterioles and capillaries in inflammation are very contradictory. Certainly inflammation in its more essential phase of capillary paralysis is not affected by isolation from the nervous system even when the nerves have degenerated and it is questionable whether such complete exclusion of the nerves affects a rather hypothetical earlier stage of active hyperæmia. The authors lean rather to a direct irritation of the vessel wall perhaps through the intermediation of local nerve endings in the wall itself.

Of course the experiments of Samuel have shown that the profound vasoconstrictor limitation of the circulation of a rabbit's ear which follows section of the auricular nerves leaving the sympathetic nerves intact, persists so that the effect of a burn is necrosis and not inflammation, while the reverse section of the sympathetics which leaves the vasodilators of the auricular nerves free to maintain a great flushing of the ear, rather favors a violent inflammatory reaction after scalding.

The attempt to define the effect of the vasomotor nerves upon the hyperæmia of inflammation which has led to the separation of an active arterial hyperæmia from a paralytic passive widening of the capillaries, ends rather lamely in the assumption of a localised nervous mechanism in the vessel walls. There is much proof, however, (Krogh) that the walls of the arterioles and more particularly those of the capillaries, have an important independent tone and contractility

so that the effect of the irritant may well be direct and without the intermediation of any nervous mechanism and further that it may well be a direct chemical influence. The work of Dale and his colleagues upon shock showed clearly that the enormous dilatation of the capillaries which produces a partial stagnation of the blood in the widened channels, is or may be due to histamine, a derivative of the protein of injured tissues. We thought it might be possible that the widening of the capillaries in inflammation could also be explained as the effect of a substance like histamine or histamine itself upon their walls and the adjacent injured tissue might well constitute a source of this histamine. Dr. Rich therefore studied the effect of histamine upon the capillaries and proved that when locally applied, or when injected into the circulation, it does widen the capillaries greatly, bringing into prominence many which were invisible before. He did not apply this result directly to inflammation but it seems to be a very plausible explanation for the paralytic condition of the capillaries found there. The rapidity of its action makes the distinction between a stage of arterial hyperæmia and one of paralytic hyperæmia seem rather questionable.

Dr. Rich's experiments showed that any attempt to examine and measure the capillaries by spreading out the omentum resulted in a maximal dilatation and paralysis of the capillaries no matter how carefully the tissue was protected and that the effect of histamine could be shown only in the omentum which had never been so exposed. This makes one question a little the accuracy of the generally accepted observations upon the slowing of the blood stream in inflammation. These observations have been made very largely in exposed tissues where extreme injury might well occur, and are rather inconsistent with the

familiar hot rush of blood through an inflamed area and also with the observation that an incision into an acutely inflamed tissue allows the escape of arterial and not venous blood. But there is at least no question that in these exposed tissues the process of emigration of leucocytes occurs only after the visible slowing of the stream and it seems difficult to believe that it could occur to the same degree if the initial rapidity of the stream were maintained.

The widening of the capillaries brings into plain view channels filled with blood which were previously invisible and existed doubtless as collapsed tubes of endothelium. The application of adrenalin appears to have no effect in contracting the vessels of an inflamed tissue and lessening the content of blood, nor has it in the case of the tissue poisoned with histamine. It appears, as was pointed out by Dale and Laidlaw that this widening is really due to a paralysis of the otherwise active endothelial cells which causes them to relax their tone and allow blood to pass and accumulate in much greater volume than before. The gradual resumption of their tone after the waning of the inflammatory process leads once more to their narrowing and in many cases to their disappearance from view.

Changes in Capillary Walls.—It seems that this paralysis is accompanied by other changes in the capillary wall which are recognisable only by their effects. The leucocytes now adhere as they pass and are only dislodged by the violence of the stream, finally remaining attached at a point at which, by forcing a pseudopod through the wall between two endothelial cells, they ultimately make their way out. It has been shown that the silvered endothelium in this condition shows broader lines between the endothelium than in the normal capillaries but we cannot recognize morpho-

logically any more significant change. Nevertheless the wall becomes much more permeable for fluids and for the proteins of the blood, since the fluid of an inflammatory exudate is much richer in protein and more readily coagulable than the transudate which appears without inflammation. The emigration of the leucocytes is aided in the slower stream by their lightness which allows them to separate themselves from the heavier axial stream of red corpuscles and flow along in the marginal zone of plasma. The change in friction between the altered endothelium and the plasma which is used as an explanation of the slowing of the stream may also facilitate the adhesion of the leucocytes. They force their way out eagerly and in all their movements are guided by the attraction exerted by the diffusion of some chemical substance from the injured tissue or from the injurious agent itself (chemotaxis). Their approach to this dead or injured tissue is otherwise incautious because they often come too near and are themselves injured or destroyed. When the source of attraction is merely a mass of dead tissue they penetrate its margins but are automatically brought to a stop by lack of oxygen. In diffuse forms of inflammation in which the injury has not been concentrated the exudate is found throughout the tissue.

Increased Temperature of Inflamed Part.—These changes explain fairly easily as remarked above, the swelling and redness of the inflamed tissue. The heightened temperature of the part is ordinarily thought to be due to the rapidity of the flow of blood which passes before it can be cooled and thus brings to the surface the temperature of the interior of the body. The inconsistency of this with the idea of slowing of the stream in the widened capillaries has already been suggested. Several writers and most

recently Segale, have tried to show that there is an increased local metabolism which is responsible for some heat production in inflamed tissues but this seems not entirely convincing and would at most account for only part of the heightened temperature.

Pain in Inflammation.—As to the pain apart from that caused at first by the direct action of the irritant we have no very satisfying explanation. Tension of the tissues would appear to play a great part since the relief of tension by incision of an abscess usually brings relief of pain. It is objected that tension produced in the interstitial injection of fluid is part of the method of local anæsthesia and that the pain in inflamed and swollen tissue must be due to irritation of the nerves by the inflammatory irritant.

Bittler thinks the pain due to insufficient vasomotor relaxation and perhaps the supposed relief from the application of heat to an inflamed area falls in with this idea, but in a tissue in which the arterioles and capillaries are widened to their utmost, vasomotor relaxation seems hardly capable of being pushed further.

Composition of Inflammatory Exudate.—At first the inflammatory exudate outside the vessels is rather simple—a fibrinogen containing and therefore coagulable fluid which soon shows interlaced fibrillæ of fibrin, neutrophile leucocytes and a few red corpuscles together with a few lymphocytes. Later if the inflammation is protracted by the persistent pressure of the irritant, as is so generally the case, there arrive other freely wandering cells which are by no means so clearly derived from the blood in the blood vessels but seem to have wandered into this region from somewhere in the neighborhood. These are in great part mononuclear cells varying in size and in their other characters. Most of them are usually larger than

lymphocytes with a more vesicular nucleus and cytoplasm which is nongranular or contains a few basophilic granules. These are the mononuclear wandering cells, monocytes, histiocytes, clasmatocytes or polyblasts of various authors. Mallory has called them endothelial leucocytes. In somewhat later stages plasma cells appear as oval or elliptical, smoothly outlined cells whose nucleus with deeply staining clumps of chromatin is placed usually at one end while the cytoplasm takes a bluish stain, leaving an unstained space about the nucleus. These are related to the lymphocytes and of lymphocytes there are usually large numbers.

With such a field for study we must pause for a little to ascertain the nature of all the cells concerned and the source of those which accumulate in unaccustomed numbers. We may distinguish at the beginning cells, which, because they are intimately bound up with others of the same sort by intercellular bridges or otherwise, remain stationary and form a tissue, from another group of freely moving cells which are bound by no ties and are either swept along in the blood or lymph or wander at will by their own powers of locomotion anywhere in the interstices of the tissues. The first, the fixed tissue cells, can of course divide and stretch out processes and by growth spread over a surface or into a scaffolding of fibrin but we see little evidence of any power of active wandering. The free wandering cells on the contrary can put out pseudopodia and travel like amœbæ at will. Rather they seem to be guided by smell or taste or something analogous for they are impelled to move in the direction of certain substances which attract them by virtue of some chemical influence radiated through the tissues for some distance. This is the process of chemotaxis which has been so much discussed by Pfeffer and by

Metchnikoff. Negative chemotaxis is thought of also as the repulsion felt by these cells for substances which act in the opposite way but there is less convincing evidence if its existence.

The nature and origin of all the fixed cells is very clear from embryological investigations. Even the most questionable, the lining cells of the peritoneum and other body cavities are now universally regarded as cells of mesoblastic origin although they participate in some of the morphological characters of epithelium. This is true of them in far less degree than of the cells of the renal tubules which everyone thinks of as epithelium although they too originate from the early mesoblast. It shows that the ultimate form and function may be quite far removed from what might be expected from the origin.

Nature of Wandering Cells.—The origin and development of the wandering cells has been the subject of interminable dispute and there are still many great problems awaiting solution but in general it may be said that in the embryo and fœtus they arise in very many regions—almost everywhere, in fact, from the tissues of the supporting framework of the body and the blood vessels. After birth it seems that certain areas become specialised for their production, among which the bone marrow comes to hold a very prominent place as the chief seat of formation of many of the cells of the blood. I shall not attempt to enter into the discussions of those who hold to the monophyletic origin of these cells as opposed to those who regard them as of dual or polyphyletic origin. Excellent, and, indeed, epoch making studies have been made by Ehrlich, Maximow, Dantchakow, Marchand and others and Pappenheim and Ferrata have collected all this information in atlases of the morphology of these cells. Such numbers of forms and so many tran-

sitions with such a variety of details of structure and types of granules have been observed that one may well become bewildered. This work has been done with various ingenious methods of isolating experimentally the interesting cells, fixing them and staining in sections or otherwise and an almost complete survey of their origin and relations has been made. But much of the tracing of the relations of cells depended upon the finding of transitional forms, which is an uncertain sort of evidence. We have, therefore, hailed with pleasure the work of Dr. Sabin which concerns the origin of the cells of the blood and connective tissue in the area vasculosa of the embryo chick. The difference between this and the other work lies in the fact that by watching the growing tissue, living cells specifically differentiated by vital stains can be seen and followed through every stage of their development. One cannot feel any doubt of the correctness of these results and it is comforting to find that most of the previous work agrees fairly well. The main results are as follows: In the undifferentiated mesenchyme certain cells in strands separate so as to contain a lumen which fills with fluid. These are angioblasts and when they thus line a canal are endothelial cells. From the endothelial cells by division cells are formed which drop into the lumen of the canal and after various developmental changes become red corpuscles. Other cells arising from the endothelium in the same way and dropping into the lumen or becoming strewn off to the outside of the endothelial tube become the monocytes or large mononuclears and transitionals of the blood and the monocytes or histiocytes or mononuclear wandering cells of the tissue. They are apparently identical with the adventitial cells of Marchand, the polyblasts of Maximow and the macrophages of Metchnikoff as well as the endothelial leuco-

cytes of Mallory. It must be remembered, however, that this proof of their origin is brought only for embryonic tissues as yet. Other cells resembling angioblasts but outside recognisable blood vessels, give rise to mononuclear granulated cells which become the various types of polymorphonuclear leucocytes. These quickly make their way into the blood vessels, passing between the endothelial cells. Dr. Sabin's work gives no idea of the origin of lymphocytes which appear to arise within the body of the embryo and not in the area vasculosa. We must, therefore, cling as yet to the idea of Flemming that they take their origin from the germinal cells of the adenoid tissue although Marchand in his review describes their derivation from indifferent wandering cells of the mesenchyme which also give rise to various other types of cell.

While these things are fairly clear in the embryo and we can believe that endothelial cells and angioblast-like cells of the mesenchyme can everywhere give rise to the mobile cells of the blood and tissues, it is not quite so clear in the adult organism. There we know that under normal conditions the formation of the red corpuscles is practically limited to the bone marrow. This is true also of the neutrophile and eosinophile leucocytes. The lymphocytes appear to arise in adenoid or lymphoid tissue everywhere but we do not yet know precisely where to locate the definitive site of formation of the monocytes, that is, the larger mononuclear cells of the blood and the larger mononuclear phagocytic wandering cells of the tissue. Marchand in a former paper referred them to the indifferent wandering cells of the mesenchyme, but in a more recent one derives many of them from endothelial cells. Aschoff and his pupils derive them from the so-called reticulo-endothelial cells of various tissues, especially the adenoid tissues and spleen and

the lines between these and the cells of the lymphocyte series are not sharply drawn. Dr. Sabin's methods seem to show, however, more clearly than ever before that the lymphocyte is a cell apart and suggest that the embryonic mode of formation of the larger mononuclear wandering cells may be perpetuated in the connective tissues or in some organ such as the spleen.

All those cells seem to diverge permanently from the fixed tissue and assume specific functions which are quite different from those of the connective tissue cells. The most distinctive are perhaps the granulocytes or polymorphonuclear leucocytes with their neutrophile or eosinophile granulations. These are so familiar that we need refer only to their ability to act as phagocytes and their especial avidity for bacteria—they produce, as Opie has shown, a proteolytic ferment which acts like trypsin in an alkaline medium. The lymphocytes are not strikingly phagocytic nor are their peculiar oval derivatives the plasma cells of Unna, but the monocytes or mononuclear wandering cells exhibit an eager power of engulfing and digesting, not so much bacteria as the debris of injured and dying cells. They, too, produce a ferment which like pepsin acts in an acid medium. It seems improbable then that the neutrophile leucocytes and the monocytes could act side by side in one fluid medium.

Activities of the Exudate.—The inflamed tissue at this stage contains much debris of the dead and injured cells together with fibrin and often bacteria and other foreign particles. All these things form an obstruction to the restoration of the tissue to its normal state by any process of repair and must be removed to the last particle. This is essentially the task of the mononuclear wandering cells which as ferment producing phagocytes now approach. They become especially numerous if the inflammatory reac-

tion is protracted by the persistence of bacterial or other irritation but seldom advance quite into the field reached by the neutrophile leucocytes where bacteria are active.

There are many forms and great extremes in size—in any old area of inflammation the collection of loose cells is really bewildering in its variety and it is little wonder that confusion has reigned so long as to their relation each to the other. Lymphocytes can readily be found in great numbers and among them many larger cells with paler nucleus and cytoplasm which varies extremely in its abundance. These larger cells are most distinctly phagocytic and may often be found loaded with the partly disintegrated bodies of other cells. Often they contain fat droplets and this is usually the case when they have grown to a very great size. They have no conspicuous specific granules but they may acquire more than one nucleus. Indeed, it seems to be from the fusion or incomplete division of these cells that most of the foreign body giant cells are formed.

These are the cells which Maximow called polyblasts and which he derived from the lymphocyte through a process of growth following upon their emigration from the blood vessel. But they correspond also as already stated with the histiocytes of Aschoff and Kiyono and with the endothelial leucocytes of Mallory.

We are left with a somewhat vague idea that even though we know they must be continuously formed throughout life and that in the embryo they arise from the capillary endothelium, their precise point of origin in the adult is not yet proven. Multiplication by mitosis in situ is often evident and gives one explanation of their increase. Special irritants attract a conspicuous number of other cells such as the eosinophile leucocytes which are abundant in the reaction

caused by worm parasites or the mast cells with basophilic granules which appear in numbers in some other infections. Plasma cells which seem to be regarded as closely related to lymphocytes are sometimes in chronic inflammations so numerous as to overshadow all the others.

In general, then, we may say that in the acuter stages of the inflammatory reaction the polymorphonuclear leucocytes with their phagocytic avidity for bacteria and their trypsin-like ferment dominate the field while in more protracted inflammatory reactions the mononuclear wandering cells make their appearance in quantities and by means of their ability to engulf the debris of cells and with the aid of their pepsin-like ferment act as scavengers and clear away all obstructions to repair.

Significance of Inflammation and Allied Reactions

The significance of all this which so far represents the inflammatory reaction seems on reflection sufficiently clear. There are numerous reflexes which serve to prevent or ward off injury such as coughing, sneezing and vomiting. There are also numerous mechanical contrivances for the protection of the body against injury, better developed in other animals than in ourselves. Inflammation differs from these in that it is a response to an actual injury which aims at the limitation of the injury and the destruction and removal of the irritant and of all the dead material left behind. It is so orderly in its progress and makes use of so many physical and chemical processes, and takes advantage so thoroughly of the peculiar fitness of such substances as fibrin to serve its ends that one can only suppose that such a wonderful mechanism must have been evolved in the course of ages through the selection of the most useful features of all possible

reactions by the survival of those animals in which they occurred.

It would be interesting to learn if we could from the fossils of the earliest periods whether inflammation existed in those days. We know well enough from Ruffer's studies of the mummies of Egypt that our familiar inflammation was perfected some thousands of years ago but it is pleasing to think that the lack of it might have had something to do with the extinction of the fearsome mesozoic reptiles.

Even now after all these centuries it is by no means a completely satisfactory process. It seems clumsy and our autopsies show how often it fails to prevail over the inroads of the injury, how often it brings about conditions which, no matter how praiseworthy the intention, are in themselves a menace. The complete obliteration of the air space of the lung in pneumonia by the inflammatory exudate or the compression of the lung and the great displacement of the heart by a massive pleural exudate, are examples, but no doubt we must be content with the thought that otherwise the man must have died long before from the direct effects of the bacteria.

Inflammation which, as we see, is a local reaction, is commonly associated with a general reaction also of a defensive nature, fever. They are independent in the sense that there may be fever without any inflammation. They are so different that we are by no means forced to include fever in our conception of inflammation but may think of it as an analogous or parallel reaction. In its complexity it also suggests a long evolution with the retention or survival of the most useful features and like inflammation, although its defects and its disturbing influence have long been uppermost in our minds, it is more and more clearly

recognised as a beneficial reaction somehow associated with immunisation and the limitation of injury.

The whole range of phenomena which we know under the general heading immunity belong here also as reactions of living beings to injury developed in such a way as to render the body safe from that particular injury in future. This safety cannot in nature be attained without suffering although we can cheat the disease of its penalties sometimes by artificial means. At best though, it is the successful struggle against the injury which fortifies the body against another such attack. Time will not permit us to discuss this subject about which a whole literature has arisen. It is interesting in connection with inflammation chiefly in that it is another member of the array of defensive reactions.

With our present knowledge it is perhaps unjustifiable to state that the process of inflammation itself brings into play the immune bodies which result from the introduction into the tissues of foreign proteins or protein poisons. That would be to assume that the fluid of the inflammatory exudate contains these immune substances in a degree effective as part of the mechanism of defense. This is hardly to be suggested in all the myriad examples of inflammation which result from some physical injury—it is hardly imaginable in the early stages of inflammation caused by bacteria in which stages the outpouring of fluid exudate is more profuse. In the late stages of a protracted inflammation caused by bacteria it is clear that immunity is developed and may turn the tide of success in resisting the infection—it is even clear as Cross showed that during a long infection opsonins in the blood increase in such a way that phagocytosis is more effective than before. But in general while the reactions of immunity come readily to the aid of

inflammation they do not form an integral part of that reaction and at most we can only say that in inflammation the fluid exudate in addition to its diluting and mechanical effect brings to bear upon the bacteria or upon the protein poisons the natural bacteriolytic and proteolytic ferments of the plasma and of the leucocytes and not except through the aid of a separate reaction the specific new formed immune bodies which arise after the lapse of time.

Interesting in this regard is the intensified inflammatory reaction in an allergic animal which has been sensitized by the introduction of some protein when the same protein is again brought into contact with the tissues. The tuberculin reaction in tuberculous animals is an example of this and so too is the flaring inflammation which follows the inoculation of tubercle bacilli in an animal which has survived an old tuberculous infection. In these cases it seems probable that the readiness of the allergic tissues suddenly to decompose these proteins into toxic proteoses is a sufficient explanation of the greatly intensified injury with its appropriate reaction. But it is not quite so simple as this for Rössle in his recent experiments shows that the tissues react with eosinophile leucocytes or with lymphocytes when the sensitizing protein is again injected and that there are peculiar stases in the vessels, excessive œdema and evidences of shock.

Regeneration and Repair

Relation to Inflammation.—So far then we find in inflammation a response to injury carried out by the flushing of the widened capillaries in the local area and the pouring out of fluid and cellular exudate to which is added an inwandering of the mononuclear phagocytic cells of the tissues which tend to clean up the devastated region. But this advent of leucocytes

and the accompanying leucocytosis in the general circulating blood as well as the swarming of the mononuclear cells suggests the necessity of a new formation of these cells. We cannot easily find the manufactory of the mononuclears but we have only to look at the bone marrow of the femur to find an intense multiplication of its blood-forming elements in progress. Some message has been sent which stimulates it to this great activity—the function to which it is specifically adapted, but still a new formation of cells in response to a demand which is really an essential part of inflammation. This touches at once upon the bitterly debated question as to the propriety of including in the conception of inflammation the new formation of tissue. To me it has always seemed that the idea of inflammation already outlined is complete and well rounded—that any new formation of fixed tissue elements, which is of course intertwined in any inflammatory reaction following destruction of tissue, is really a separate and different kind of process, belonging more strictly to the conception of regeneration and concerned in this instance with the repair of the cells which were lost. If we transfer our attention to such processes of new formation of tissue as are found in the compensatory enlargement of half the liver when the other half is removed, or of one kidney when the other is extirpated, we have new growth without any trace of inflammatory reaction. Indeed the hypertrophy of the heart or of any other functioning organ when more work is put upon it, illustrates this and unless we can show that the new growth of tissue which occurs in an inflamed area is a direct result of the injury and defensive in nature, it seems hardly incumbent upon us to include it within the limits of inflammation.

But the very effort to assign reasons which would

make it necessary to group inflammation and new formation of tissue under one name shows how unimportant it is to make sharp frames for each conception because they are after all rather arbitrary groups of phenomena. The recent literature is largely devoted to arguments as to the definition of inflammation—Aschoff would include in it every defensive reaction—others would abandon the term altogether. Practically all authors except perhaps Neumann and Borst include new formation of tissue under inflammation without any hesitation. Neumann separates them to some extent and Borst speaks of inflammatory new formation as somewhat distinct from regeneration in general and cites many examples of chronic inflammatory processes in which excessive new formation of tissue is indissolubly associated with inflammation, as in elephantiasis. He regards such inflammatory new formation as in the nature of organisation—the growing into or about foreign or dead materials. This is not a direct result of a stimulus but an indirect one due to an increase in the function of these cells.

Under any condition we are clear enough as to the phenomena themselves—the inflammatory vascular reaction which is directly responsible for the recognised cardinal symptoms, forms one convenient group; the regenerative new formation of tissues in whatever place and for whatever purpose form another convenient group. The latter occurs constantly without any participation of the former and there are also many examples of inflammation with little or no appreciable new formation of tissue (unless we include the leucocytosis). No compelling facts seem to exist which force us to associate the growth of tissue with the defensive inflammatory reaction and, therefore, for convenience sake it seems permissible and preferable to hold them separate as abstractions from the

complex mixture of phenomena which is usually found.

Marchand in his most recent paper (1921) gives the following definition of inflammation.

"We understand, therefore, by 'inflammation,' 'inflammatory' a series of reactive processes on the part of the vessels and the tissues which after the action of injuries of physical, chemical and infectious character pursue an orderly course and in favorable cases lead to the abatement of the injury and thereby to healing (Biological definition).

"Acute inflammation is initiated and characterised by local hyperæmia, widening of the small vessels, irritative arterial hyperæmia with increased blood stream through the part, upon which follow slowing of the circulation, paralysis and increased permeability of the walls of the small vessels, which with constant participation of the elements of the tissue lead to the formation of a coagulable exudate more or less rich in cells.

"We define as chronic inflammatory processes those which proceed with continuous exudate formation and with conspicuous tissue growth, especially of the vessels and connective tissues and which either arise from acute inflammation or without this develop gradually when there is protracted injury of the tissue."

Healing.—The healing process depends upon a new formation of the cells of the tissue to replace those which have been destroyed and thus to make good a defect whose size is usually rapidly decreased by contraction during the completion of this new formed tissue. Perhaps the simplest example is found in the healing of a wound with actual loss of tissue which must be filled up by new tissue. The injury in itself is sufficient even without infection to excite an inflammatory reaction. Blood escapes upon the surface of the exposed tissue and clots, or if this be removed the

inflammatory exudate continues to escape and clot on this surface. Growth of tissue begins in due time by division of the cells a little way back from the actual surface or from the edge of the epidermis. New connective tissue cells are formed and sprouts from the capillaries whose ends have been interrupted in the wound and finally plugged by thrombi. Together these capillaries and fibroblasts thrust forward toward the surface, penetrating the overlying blood clot or the fibrin of the coagulated exudate and digesting it away. The leucocytes of the exudate and the mononuclear wandering cells are present in numbers and injury from persistent bacteria may cause a further exudate formation from the new capillaries, but gradually, except when the bacteria are very tenacious of life, the surface of the new tissue becomes clean and all the fibrin and cell refuse through which it has grown are removed. The tissue has a rough granular surface (granulation tissue) and is œdematous and infiltrated still with wandering cells. It is extraordinarily rich in blood vessels, soft and easily made to bleed but now very resistant to the further invasion of bacteria. Even before it reaches the level of the skin multiplication of epithelial cells pushes forward the edge of the epidermis and a thin bluish film of new epithelial cells creeps from every side over the granulation tissue, covering it smoothly. Then with this protection the inflammation fades away, the fibroblasts and intercellular fibres increase while the capillaries diminish in number so that finally a dense scar of gradually increasing pallor is formed. It requires a long time before such a scar is reorganized by the ingrowth of nerves, the formation of papillæ in a new corium, etc., and it is only the oldest scar that approaches the normal appearance of the original tissues at that site. Quite similar is the healing in the

peritoneum when two loops of intestine are glued together by fibrin after infection and injury and an acute peritonitis. Blood vessels and fibroblasts grow through the fibrin, eating it away and absorbing it until they meet and fuse with their fellows of the opposite side. Peritoneal lining cells cover on all sides this new fibrous adhesion which may be short and thick but sometimes mechanically stretched out into a thin veil-like sheet.

Healing in a tissue where there has been necrosis of a mass of cells with diffuse surrounding inflammation proceeds in the same way as soon as the site is tenable for the new capillaries and fibroblasts. Often it goes in advance of this cleaning up and purification and the advancing capillaries are blocked and destroyed by the still present bacteria. Even when the way is cleared by the phagocytes and their ferments and the necrotic tissue liquefied and absorbed, there may be a cavity left filled with fluid, but the new cells by growing forward and drawing together, soon obliterate this cavity. Leucocytes may pass back into these capillaries but often they have suffered such injuries that they themselves are swallowed and destroyed by other cells or liquefied by their ferments.

Nature of Repair.—The outstanding problem at this stage is that of the reasons for the new formation of cells and the workmanlike repair of the defect. We have been able to find some sort of plausible reason for the widening of the vessels and the outward rush of leucocytes and fluid although it is true that we have not been able to explain these things on purely physical or chemical grounds but in each instance have left an element of irritability of the living cell which is a mystery. When we say that the leucocytes make haste toward bacteria or other irritants on account of a chemiotactic attraction, it is conceivable that some

day we may be able to explain this as a phenomenon of surface tension which is affected more and more strongly by the diffusing material as the leucocyte enters into zones of greater concentration, but this proves a rather inadequate explanation of the observed fact that a leucocyte may be gradually accustomed to some substance which at first repels it so that afterward it is attracted. When we find that the tips of the lashes of endothelium which are to form blood-vessels meet precisely and unite like the ends of a tunnel bored by a skilful engineer from opposite sides of a river, we say once more that it is a chemiotactic process. It seems easier to believe that as Clark described it, they wave about until they touch each other and then unite.

But when we come to consider the new growth of blood vessels, of fibroblasts and of epithelium which serve to fill the gap, the mysteries are even more profound and we are forced to a conception of a foreordained plan which continues to control all growth not only in the individual but in all individuals of that species. It is as though all repairs were made by reference to the original builders blueprints. The repairs may be awkwardly carried out but in the end it approaches the plan because the tissues are never content but continue to modify the area of healing until its site can hardly be found and it is merged into the normal relations. Naturally this requires a long time and many people die with the restoration still incomplete, but in adult life it is hard to find the point at which a bone was broken in childhood and the scars of slighter injuries are often more quickly obliterated. It seems that a very precise equilibrium of tissues is reached in the normal body. This is true from a functional point of view as everyone knows but it is also true structurally. The right side of the heart throws

out into the arteries of the lungs exactly the same number of drops of blood at each beat as the left side throws into the aorta and there is little doubt, although I have not the figures to show it, that the ratio of fibres in the wall of the right ventricle to those of the left is a mathematical constant. So, too, the relation of the number of cells in the liver to those in the kidneys is probably a constant and the loss of one hundred liver cells must be felt as a disturbance of equilibrium. This must be a functional equilibrium, but it may be maintained by a restoration of those cells to the proper number. It is possible, also, that aside from tissues which have such important chemical functions there may be a physical equilibrium in the supporting tissues so that when a stretch of fascia is interrupted by an injury, equilibrium is not restored until it is repaired and the normal tension re-established.

Theories of Causes of Tissue Growth.—This idea, which may be applied in its details to every tissue in the body, is the basis for Weigert's conception of the reason for the new growth of tissue after injury. Virchow had assumed a formative stimulus exerted by the irritant directly upon the cell and causing it to grow. Weigert hotly contested the possibility of such an effect and claimed that in all cases the impulsion to growth came from the disturbance of equilibrium due to the loss of other cells, the sense of defect or, in its simplest form (although this was more definitely the idea of Ribbert) the relaxation of the pressure or tension put upon the adjacent living cells which are capable of division and growth. But the power of growth itself was inherent in the cell and represented a part of the energy transmitted to it as an inheritance from the great store of energy of the fertilised ovum. Virchow thought of a direct chemical

or physical stimulus to growth. Such a stimulus could hardly be thought of as contributing the energy which is revealed in the actual growth—if not, it could only, like the trigger of a gun, let loose the energy of the cell—change its function to the extent of stirring it to absorb more nutrition and apply more energy to growth. It might even be regarded as the removal of an inhibition which prevented the cell from carrying on this natural absorption of nutrition, formation of new chromatin and cytoplasm and division. In this sense a formative stimulus is not very different from a disturbance of equilibrium since in both cases an inherent power of the cell is let loose.

The practical difference in the application of these two ideas which still struggle for supremacy is that with cell growth the result of a chemical or physical formative stimulus, Virchow need not hesitate to conceive of the process of cell division and growth proceeding to the formation of any quantity of new tissue. Weigert ought to be at a loss for an explanation of any growth beyond that necessary to re-establish the equilibrium.

But everyone knows that excessive growth of tissue occurs. Granulation tissue may grow far out of a healing wound and project on the surface, an old pleurisy ends in a scarred mass all round the lung a centimetre thick, a cirrhotic liver may contain broad bands of dense fibrous tissue which fairly creak when cut through. Weigert was forced to assume that the response to the need of repairing the defect often overshot the mark in simple healing and later repaired this fault by reducing the tissue to normal limits. The explanation of the thick scarred pleura is even more difficult but if it be attempted upon the idea that the persistence of bacteria frustrates each attempt at healing so that it soon comes to be a question of heal-

ing defects in new-formed tissue, and the layers pile up, we must still assume that each new healing over fills the actual defect—otherwise there would be no piling up of layers and only when the last layer was permanently laid would the original level be reached. In the case of the pleura this would be a pretty thin layer.

On the whole it seems that the attempt at the orderly restoration of the body form in every detail is an underlying process which makes its influence felt ultimately—but that may be a different thing from that which causes the immediate new growth of tissue. The underlying tendency would replace the tissue as it was, the immediate new growth of tissue far more often substitutes something not quite as good—it repairs with the ever ready connective tissue.

What are we to think about the new formation of tissue which is so often—almost regularly—interlaced with the phenomena of inflammation after an injury? Is it purely a response of the underlying tendency to make good the cells which have been destroyed? Is it due strictly to the disturbance of physical or functional equilibrium? In that case it ought to replace each tissue exactly and no more. But it substitutes in the interim a mass of fibrous tissue which can hardly be a response to the loss of functional equilibrium in areas previously composed of working epithelium, as in the liver. Must we then think that the injury acts as a direct stimulus to these bystanders among cells to stir them to growth or at least let loose their energy of growth as a mechanism of quick repair and protection of the exposed injured area? Perhaps this fibrous tissue is always tending to grow to excess and is only held in check by the surrounding cells so that instead of a formative stimulus it is merely left free to grow. Or may we think of it all as merely a blind

response of the fibrous tissues and the blood vessels and the overlying epithelium to the tactile and chemical stimulus offered by fibrin and dead tissue through which, and over which, they grow.

It is hard to decide and after all it seems a scholastic argument about a very small point which, in the end, may not depend on a very real difference between the views.

Relation of Repair and Regeneration to Embryonic Development.—The actual process of growth under these disturbed conditions is, nevertheless, of great interest. When a cell is killed naturally all its functions cease but when it remains alive, though injured, and shows some of the retrogressive changes which we have already described, it is a question as to how far it is able to undertake the complex effort of absorbing new materials of nutrition and dividing into two. One sometimes finds mitoses in cells which lie in a zone which is exposed to injury and which themselves show inclusions of fat droplets which are supposed to indicate in such a case a retrogressive change. We are less surprised to find evidences of rapid growth in cells somewhat further removed from the line of injury. But any injury must impair in some way these cells although perhaps we may say that it only disturbs them. Borst thinks of three processes as characteristic of the cell: nutrition, multiplication, and its specific function. If, then, the disturbance impairs the specific function, the cell may still be even more ready to assimilate nutriment and to divide. But in general he assumes that assimilation and division are the direct outcome of increased function as seen very clearly in the rapid growth of a kidney when the other is removed, or in the hypertrophy of a heart when it is overworked. And he points out the impressive fact that no physical machine which we could imagine our-

selves constructing would have the unique property of growing and increasing its power or even of producing several new machines of equal power through being overworked.

The power of the tissues to grow depends upon a vital property which our knowledge of physics and chemistry has not yet allowed us to explain. This property is present in perhaps the supreme degree in the fertilised ovum which is about to segment and as the segmentation proceeds its several elements are transmitted to successive generations of cells in decreasing intensity—the power of assimilating nutriment persists, the power of multiplication rapidly decreases, the power of differentiation into specialised cells with different functions is quickly reduced to unipotence, or the ability to reproduce only its own kind. The ovum is totipotent but there is a gradual loss of the ability to differentiate until the cell becomes unipotent and unable to differentiate itself any further. But not all tissues are reduced to absolute unipotence from the state of multipotence which they enjoyed in the embryo, for there are some, such as the endothelial cells of the bone marrow, which in the adult are able to give rise to several kinds of blood cells. The very ability to multiply is better preserved here than elsewhere but there are also other zones of proliferation such as the Malpighian layer of the epidermis, which throughout life seems to be actively replacing cells which are lost from the surface.

Phylogenetically the power of regeneration is diminished and the regeneration of extensive and complex structures which occurs so readily in the lower animals is lost to us. But tissue can be reproduced by the multiplication of remnants of tissue of the same kind. So long as any of the unipotent differentiated tissue remains it can form more of the same kind but there

is little evidence of the formation of any highly differentiated tissue such as the cells of the liver or kidney from anything which had never reached that stage before the emergency demand for new tissue arose. Thus, it is extremely rare to find any satisfactory evidence of the development of new liver cells from the stumps of bile ducts although remnants of differentiated liver cells produce them in abundance.

Tissues are thus able to regenerate without much new differentiation and the frequent references made to a return to the embryonic state in connection with the newly formed cells in the repair of an injury seem unjustified since these tissues apparently only reproduce their kind without any return of a power of differentiation into cells of other specialised function. At least so it would appear although we are not quite certain that the new blood vessels of granulation tissue cannot once more assume the power of forming from their freshly grown endothelial cells new mononuclear wandering cells which may swell the host that we find collected there.

The more highly differentiated and specialized in its function the cell, the less in general is its power of reproducing itself and it is for this reason that defects in voluntary muscle and heart muscle and in the brain are filled up by fibrous tissue, or neuroglia in the case of the brain, which is their only substitute for a long time.

We are not interested here in the general subject of regeneration but only in so far as it has a bearing upon the completion of the fate of an injured area in which inflammation has played its part.

Course of Inflammation in Various Infections and Other Injuries

Let us examine then a few concrete examples of different effects of injury with inflammation or repair,

to see how these processes are illustrated and how they are interrelated.

Pneumonia.—Acute lobar pneumonia caused by the invasion of the pneucococcus is the result of the direct injury of the epithelial cells which line the bronchi, the bronchioles and alveoli, and of the underlying connective tissue and capillary blood vessels. The response to this injury is, after the desquamation of some of the injured epithelium, the pouring out into the air spaces of a great quantity of fluid, leucocytes and red corpuscles with the rapid coagulation of this fluid. The affected part of the lung becomes consolidated. Various alterations occur in sequence in the color and consistency of the exudate, the red corpuscles fade and the leucocytes become relatively more numerous. Through their digestive activities they dissolve the whole exudate after the point is turned at which the protective immunization of the patient ensures recovery and the destruction of the bacteria. The liquefied exudate is partly removed by coughing, partly by absorption through the lymphatics and the restoration of the lung to normal is completed by the reformation of the epithelial cells which were destroyed. Otherwise there is practically no new formation of tissue and pneumonia of this character is a fairly pure example of inflammation very little intermixed with reparatory processes. But if anything delays for a long time the liquefaction of the exudate (and this may be due to an unusual flooding of the tissue with the antiferments of the blood) the clot becomes invaded by new vascular connective tissue, just as in the healing of a wound, and the air spaces of the lung permanently obstructed by this new tissue. Organisation in pneumonia is, therefore, not a favorable outcome and seems to be prevented ordinarily by some process which has been explained by Kline as

the result of the compression of the blood vessels and the withholding from the area, of the blood which is rich in an antienzyme capable of preventing the solution of the exudate.

Abscess Formation.—An abscess is formed when bacteria, through remaining closely clumped together, radiate from a point a very concentrated destructive effect. Staphylococci often do this perhaps in virtue of this tendency to grow in a solid mass and are soon completely surrounded by dead and coagulated tissue. The inflammatory reaction which arises on all sides sends its exudate of fluid and leucocytes toward this centre or core of dead tissue and liquefaction of the margin of the dead tissue and of the dying leucocytes occurs so that a cavity is formed, filled with pus in which the central core is isolated. If the abscess bursts or is laid open, the central dead mass which is still solid is removed together with most of the bacteria. The wall of the cavity is by this time a beginning granulation tissue through which leucocytes are still wandering and in which numerous large mononuclear phagocytes are lodged loaded with fragments of cells and fat globules. The ultimate fate of such a cavity is much like that of any open or infected wound. It is gradually cleaned and contracted and is filled up from the base by granulation tissue which forms a dense scar. But if a deep seated abscess is never opened the bacteria may in time be overcome by the fluids of the body and the exudate gradually inspissated and invaded by phagocytic cells and by granulation tissue so that ultimately a radiate scar is all that remains.

Fate of Foreign Bodies in Tissues.—If, in an inflamed wound a fragment of foreign material remains, such as a piece of sponge or of gauze, the part played by leucocytes in combating this unusual obstruction to the healing of the wound is rather

temporary. They are soon relieved by the mononuclear phagocytes which apply themselves in great numbers to the task of removing the obstacle and swarm over every filament or particle. They attempt to engulf it but failing this spread their bodies about it and become in this process larger and multinucleated so that the filaments of gauze are soon seen to be clasped on all sides by huge foreign-body giant cells. With these a new granulation tissue associates itself and the foreign particles become encapsulated in a fibrous coating and thus eliminated from any direct contact with the rest of the tissue. Any foreign body is treated in this way but some prickly particles, such as lycopodium grains or the siliceous bodies of diatoms seem to be particularly capable of calling out great numbers of these voracious cells.

Inflammation in Chronic Infection.—The process in a continually infected defect in the tissue results in a protracted repetition of the injury and of the inflammatory reaction with a long continued persistence of the obstructions in the way of healing—even the new tissue which is formed in the process of healing is continually injured and partly destroyed and must be reformed. The result in such cases is usually the condensation of the scar tissue formed by whatever survives of the granulation tissue while new granulation tissue arises on top of it. Layer after layer is thus laid down while the infected surface is still producing granulation tissue. Excessive tissue formation is thus a result of such longstanding infection. Excessive epithelial growth at the margins of the ulcer where its spread has been frustrated is of the same character.

When the infection has lasted for many years, always accompanied by a smouldering inflammation, and especially where circulatory disturbances have been associated as in elephantiasis, the most colossal

excessive growths of tissue can occur, the whole subcutaneous connective tissue becoming enormously increased, often with added papillary outgrowths covered by hyperplastic epithelium. Although this disease has long been regarded as due to obstruction of the lymphatics by mature and larval filariæ, the impression is gaining ground that much of it is really the result of streptococcal infections of the skin repeated through many years.

Chronic Inflammations.—It is important at this point to refer to such processes as are familiar in the case of cirrhosis of the liver, chronic nephritis, chronic fibrous myocarditis, etc. All of these, although designated by a name which involves the idea of inflammation, are really hardly examples of inflammation. In each instance there is the direct and repeated effect of an injury with disturbance and destruction of the functioning tissue, the removal of which causes collapse of the framework of the organ and the replacement of the lost tissue by scar. Inflammation may, of course, be associated but in the more slowly and insidiously produced examples of cirrhosis or chronic nephritis with shrinkage of the kidney there is at no time any pronounced inflammatory process. In these cases the functional disturbance is usually dependent more upon direct alterations of the functioning cells which we cannot recognise with the microscope, than upon the loss of those cells which we can recognise. What we see in an old scarred liver or kidney is not so much the direct injury responsible for the impairment of function as the gaps in the tissue and the attempts at repair and regeneration of the tissue.

But a great deal of new connective tissue is produced and the question as to the stimulus for its formation remains, although we feel sure that it has a direct reparatory trend.

Tuberculosis and Allied Diseases.—This question is even more difficult in the case of certain specific bacterial stimuli such as are found in tuberculosis, leprosy, syphilis, etc., in which there are peculiar forms of inflammation often with very little of the exudative process but with the calling out of many mononuclear phagocytes and later the extensive new formation of tissue. In some, as in the case of the miliary tubercle, the original injury and the infinitesimal primary inflammatory reaction have finally been demonstrated by Wechsberg for the support of Weigert's doctrine of primary injury and disturbance of equilibrium—but the rapid and more conspicuous response to the invasion of the tubercle bacilli is in the formation of a nodule of new tissue of peculiar type with concentric cells which may be of the nature of mononuclear wandering cells often with a multinucleated giant cell.

Influence of Internal Secretions on Growth.—All who discuss the subject of new formation of tissue are impressed by the extraordinary growths which occur at puberty when the interstitial glands of the genital organs begin to circulate their secretion. Analogous to this are such tissue growths as are associated with pathological disturbances of the organs of internal secretion—hypophysis, adrenal, etc.—The tale of these is too long to be recounted here but in general in such a condition as acromegaly it appears that some chemical disturbance has directly stimulated a great new formation of tissue. So, too, in connection with great bronchiectatic cavities in the lungs from which decomposition products are absorbed, we see extraordinary new formation of bone and other tissue in the extremities.

Influence of Chemicals on Growth and Repair.—Fischer's experiments with Sudan and Scharlach R.

which are now familiar, through the work of Davis and others, to all who deal with plastic surgery, show a remarkable effect upon the growth of epithelium and other tissues from the application of these fat soluble substances and the work of the Japanese who by rubbing crude tar upon the skin have stirred up tumor like growths of epithelium is equally remarkable. Whether this should be ascribed to a removal of inhibition or to a direct stimulation it is scarcely yet possible to say. Even more interesting, although so common as to be overlooked, is the extraordinary effect of the growth of epithelial cells in a cancerous tumor in commandeering the new formation of a connective tissue stroma with blood vessels and lymph vessels and a perfect organisation. In this we have above all other examples, it seems, the acme of the phenomenon of the pathological new formation of tissue—only less wonderful and mysterious than the malignant growth of the epithelial cells themselves.

We are confronted in these situations with the problems of living cells which are as yet insoluble for us. It is to be hoped that the researches of approaching years will go far to clear up this most mysterious process of the growth of tissue and the physical and chemical conditions which underly it.

Review

In retrospect, then, we feel that injury sufficiently intense to cause the destruction of cells and the irritation or disturbance of others calls out the defensive mechanisms of the body, among which we recognise inflammation, fever and the production of immunity by its various means. Among these defensive reactions inflammation is a local but a well-rounded one carried out by the vascular tissues which arrange the flushing of the injured area and its flooding with the protective

elements of the blood. Leucocytes and wandering mononuclear cells are concentrated there and limit and annul the injury, finally removing the debris. They are necessarily manufactured in excess in the bone marrow and elsewhere to accomplish this duty when the injury is extensive.

After this comes the process of new formation of tissue for repair of the injury but this seems a process belonging to a different category and carried out on other and different principles by quite different structural elements. Nevertheless, the two are so closely interlaced in any individual case that it requires an effort of thought to outline the abstraction inflammation from that of repair.

BIBLIOGRAPHY

1. Aschoff: Ziegler's Beiträge, 1921, LXVIII, I.
2. Kreibich: Angioneurotische Entzundung Wien, 1905.
3. v. Hansemann: Medizinische Klinik, 1920, XVI, 247.
4. Marchand: Virch. Archiv, 1921, CCXXXIV, 245.
   Dtsch. Med. Woch., 1921, Nr. 40.
5. Breslauer: Ctbl. f. Chir., 1920, XLVII, 1104.
6. Jores: Frankf. Ztschr. f. Path., 1920, XXIII, 333.
7. Clark: Am. J. Anat., 1919-20, XXVII, 221.
8. Borst: Ziegler's Beiträge, 1919, LXIII, 725.
9. Herxheimer: Ziegler's Beiträge, 1919, LXV, I.
10. Lubarsch: Berl. Kl. Woch., 1917, Nr. 47.
11. Groll: Verh. Dtsch. Path. Gesellsch., 1921.
12. Neumann: Ziegler's Beiträge 1917-18, LXIV, J